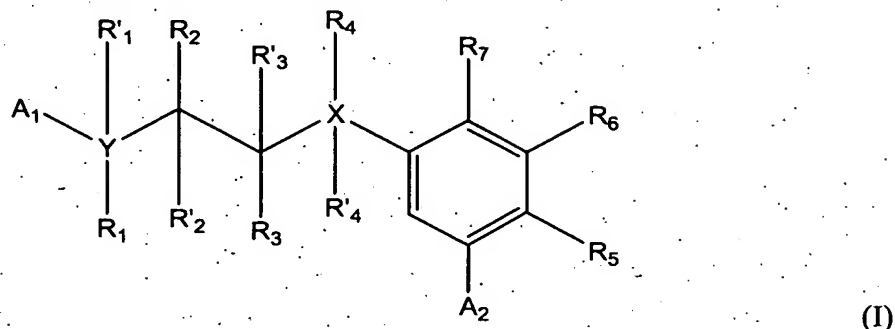


The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A compound having the structure:



wherein:

X and Y are independently selected from the group consisting of nitrogen, oxygen, and optionally substituted carbon;

A₁ and A₂ are optionally substituted aryl, arylamino, aryloxy or heteroaryl;

R₁, R₂, R₃ and R₄ are independently selected from the group consisting of hydrogen, hydroxyl, and optionally substituted loweralkyl, cycloloweralkyl, alkylaminoalkyl, loweralkoxy, amino, alkylamino, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, heteroarylcarbonyl, heteroaralkylcarbonyl, aryl and heteroaryl;

R'₁, R'₂, R'₃ and R'₄ are independently selected from the group consisting of hydrogen, and optionally substituted loweralkyl;

R₅, R₆ and R₇ are independently selected from the group consisting of hydrogen, hydroxy, halo, carboxyl, nitro, amino, amido, amidino, imido, cyano, and substituted or unsubstituted loweralkyl, loweralkoxy, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, heteroarylcarbonyl, heteroaralkylcarbonyl, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkylaminocarbonyloxy, arylamino-carbonyloxy, formyl, loweralkylcarbonyl, loweralkoxycarbonyl, aminocarbonyl, aminoaryl, alkylsulfonyl, sulfonamido, aminoalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroaralkylamino, alkylcarbonylamino, alkyl-aminocarbonylamino, arylaminocarbonylamino, aralkylcarbonylamino, hetero-

aralkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, amidino, cycloalkyl, cycloamido, cyclothioamido, cycloamidino, heterocyclyl, heterocycloamidino, cycloimido, heterocycloimido, guanidinyl, aryl, biaryl, heteroaryl, heterobiaryl, heterocyclo, heterocycloalkyl, arylsulfonyl and arylsulfonamido;

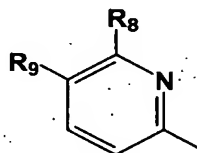
and the pharmaceutically acceptable salts thereof.

2. A compound of claim 1 wherein at least one of X and Y is nitrogen.
3. A compound of claim 2 wherein one of X and Y is nitrogen and the other of X and Y is optionally substituted carbon.
4. A compound of claim 2 wherein one of X and Y is nitrogen and the other of X and Y is oxygen.
5. A compound of claim 2, wherein both X and Y are nitrogen.
6. A compound of claim 1, wherein at least one of A₁ and A₂ comprises an aromatic ring having from 3 to 10 carbon ring atoms and optionally 1 or more ring heteroatoms.
7. A compound of claim 6, wherein at least one of A₁ and A₂ is optionally substituted carbocyclic aryl, arylamino or aryloxy.
8. A compound of claim 6, wherein at least one of A₁ and A₂ is optionally substituted heteroaryl.
9. A compound of claim 6, wherein at least one of A₁ and A₂ is selected from the group consisting of substituted or unsubstituted phenyl, phenylamino, phenoxy, pyridyl, pyrimidinyl, thiazolyl, indolyl, imidazolyl, oxadiazolyl, tetrazolyl, pyrazinyl, triazolyl, thiophenyl, furanyl, quinolinyl, purinyl, naphthyl, benzothiazolyl, benzopyridyl, and benzimidazolyl.

10. A compound of claim 6, wherein at least one of A₁ and A₂ is substituted with at least one and not more than 3 substitution groups.

11. A compound of claim 10, wherein said substitution groups are independently selected from the group consisting of nitro, amino, cyano, halo, thioamido, amidino, oxamidino, alkoxyamidino, imidino, guanidino, sulfonamido, carboxyl, formyl, loweralkyl, haloloweralkyl, loweralkoxy, haloloweralkoxy, loweralkoxyalkyl, loweralkylaminoloweralkoxy, loweralkylcarbonyl, loweraralkylcarbonyl, lowerheteroaralkylcarbonyl, alkylthio, aminoalkyl and cyanoalkyl.

12. A compound of claim 8 wherein A₁ has the formula:



(II)

wherein R₈ and R₉ are independently selected from the group consisting of hydrogen, hydroxy, nitro, amino, cyano, halo, thioamido, amidino, oxamidino, alkoxyamidino, imidino, guanidiny, sulfonamido, carboxyl, formyl, loweralkyl, aminoloweralkyl, loweralkylaminoloweralkyl, haloloweralkyl, loweralkoxy, haloloweralkoxy, loweralkoxyalkyl, loweralkylaminoloweralkoxy, loweralkylcarbonyl, loweraralkylcarbonyl, lowerheteroaralkylcarbonyl, alkylthio, aryl and, aralkyl.

13. A compound of claim 12, wherein A₁ is selected from the group consisting of aminopyridyl, nitropyridyl, aminonitropyridyl, cyanopyridyl, cyanothiazolyl, aminocyanopyridyl, trifluoromethylpyridyl, methoxypyridyl, methoxynitropyridyl, methoxycyanopyridyl and nitrothiazolyl.

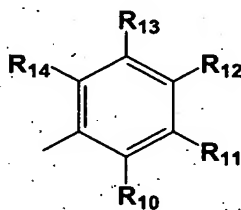
14. A compound of claim 1, wherein at least one of R₁, R₂, R₃ and R₄ is substituted loweralkyl selected from the group consisting of haloloweralkyl, heterocycloaminoalkyl, and loweralkylaminoloweralkyl.

15. A compound of claim 14, wherein at least one of R₁, R₂, R₃ and R₄ is loweralkylaminoloweralkyl.

16. A compound of claim 14, wherein R₁, R₂, and R₃ are hydrogen and R₄ is selected from the group consisting of hydrogen, methyl, ethyl, aminoethyl, dimethylaminoethyl, pyridylethyl, piperidinyethyl, pyrrolidinyethyl, piperazinylethyl and morpholinylethyl.

17. A compound of claim 1, wherein at least one of R₅, R₆ and R₇ is selected from the group consisting of substituted and unsubstituted aryl, heteroaryl and biaryl.

18. A compound of claim 17 wherein at least one of R₅, R₆ and R₇ is a substituted or unsubstituted moiety of the formula:



(III)

wherein R₁₀, R₁₁, R₁₂, R₁₃, and R₁₄ are independently selected from the group consisting of hydrogen, nitro, amino, cyano, halo, thioamido, carboxyl, hydroxy, and optionally substituted loweralkyl, loweralkoxy, loweralkoxyalkyl, haloloweralkyl, haloloweralkoxy, aminoalkyl, alkylamino, alkylthio, alkylcarbonylamino, aralkylcarbonylamino, heteroaralkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, aminocarbonyl, loweralkylaminocarbonyl, aminoaralkyl, loweralkylaminoalkyl, aryl, heteroaryl, cycloheteroalkyl, aralkyl, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, arylcarbonyloxyalkyl, alkylcarbonyloxyalkyl, heteroarylcarbonyloxyalkyl, aralkylcarbonyloxyalkyl, and heteroaralkcarbonyloxyalkyl.

19. A compound of claim 18 wherein R₁₀, R₁₁, R₁₃, and R₁₄ are hydrogen and R₁₂ is selected from the group consisting of halo, loweralkyl, hydroxy,

loweralkoxy, haloloweralkyl, aminocarbonyl, alkylaminocarbonyl, morpholino, piperidino and cyano.

20. A compound of claim 18 wherein R_{11} , R_{13} , and R_{14} are hydrogen and R_{10} and R_{12} are independently selected from the group consisting of halo, loweralkyl, hydroxy, loweralkoxy, haloloweralkyl, morpholino, piperidino and cyano.

21. A compound of claim 18 wherein R_{10} , R_{11} , R_{13} , and R_{14} are hydrogen and R_{12} is heteroaryl.

22. A compound of claim 18 wherein R_{10} , R_{11} , R_{13} , and R_{14} are hydrogen and R_{12} is a heterocycloalkyl.

23. A compound of claim 18 wherein at least one of R_{10} , R_{11} , R_{12} , R_{13} , and R_{14} are halo and the remainder of R_{10} , R_{11} , R_{12} , R_{13} , and R_{14} are hydrogen.

24. A compound of claim 18 wherein at least one of R_{10} , R_{11} , R_{12} , R_{13} , and R_{14} are selected from the group consisting of morpholino, piperidino, and the remainder of R_{10} , R_{11} , R_{12} , R_{13} , and R_{14} are hydrogen.

25. A compound of claim 18 wherein at least one of R_5 , R_6 , and R_7 is selected from the group consisting of dichlorophenyl, difluorophenyl, trifluoromethylphenyl, chlorofluorophenyl, bromochlorophenyl, bromofluorophenyl, ethylphenyl, methylchlorophenyl, ethylchlorophenyl, imidazolylphenyl, cyanophenyl, morpholinophenyl and cyanochlorophenyl.

26. A compound of claim 1, wherein R_6 is substituted alkyl selected from the group consisting of aralkyl, hydroxyalkyl, aminoalkyl, aminoaralkyl, carbonylaminoalkyl, alkylcarbonylaminoalkyl, arylcarbonylaminoalkyl, aralkyl-carbonylaminoalkyl, aminoalkoxyalkyl and arylaminoalkyl.

27. A compound of claim 1, wherein R_6 is substituted amino selected from the group consisting of alkylamino, alkylcarbonylamino, alkoxycarbonylamino, arylalkylamino, arylcarbonylamino, alkylthiocarbonylamino, arylsulfonylamino,

heteroarylamino, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, aralkylcarbonylamino, and heteroaralkylcarbonylamino.

28. A compound of claim 1, wherein R_6 is selected from the group consisting of unsubstituted or substituted aminocarbonyl, alkyloxycarbonyl, aryloxycarbonyl, aralkyloxycarbonyl and alkylaminoalkyloxycarbonyl.

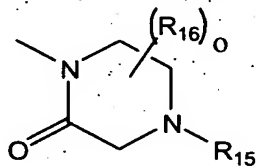
29. A compound of claim 1, wherein R_6 is selected from the group consisting of amidino, guanidino, cycloimido, heterocycloimido, cycloamido, heterocycloamido, cyclothioamido and heterocycloloweralkyl.

30. A compound of claim 1, wherein R_6 is aryl.

31. A compound of claim 1, wherein at least one of R_5 , R_6 and R_7 is a substituted or unsubstituted heteroaryl or heterocyclyl group.

32. A compound of claim 31, wherein at least one of R_5 , R_6 and R_7 is selected from the group consisting of substituted or unsubstituted pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, pyrazinyl, thiazolyl, indolyl, imidazolyl, imidazolidinyl, oxadiazolyl, oxazolidinyl, oxazolidinonyl, tetrazolyl, pyrazinyl, pyrazolidinyl, piperidyl, piperazinyl, morpholiny, triazolyl, thienyl, furanyl, quinoliny, pyrrolylpyridyl, pyrazolonyl, pyridazinyl, benzothiazolyl, benzopyridyl, benzotriazolyl, and benzimidazolyl.

33. A compound of claim 32 wherein at least one of R_5 , R_6 and R_7 is a monoketopiperazinyl group having the structure:



(IV)

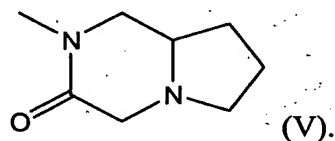
wherein R_{15} and R_{16} are independently selected from the group consisting of hydrogen, loweralkyl, loweralkynyl, aryl, heteroaryl, arylloweralkyl, loweralkylarylloweralkyl, haloloweralkyl, haloarylloweralkyl carbocyclic and

heterocyclic; or R_{16} can be taken with another R_{16} or with R_{15} to form a carbocyclic, heterocyclic or aryl ring; and o is an integer between 1 and 3.

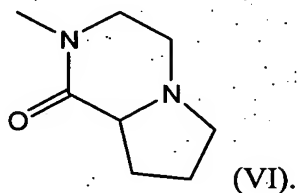
34. A compound of claim 33, wherein R_{15} is loweralkyl

35. A compound of claim 34, wherein R_{15} is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, cyclopropyl, n-butyl, iso-butyl and t-butyl.

36. A compound of claim 33, wherein R_{15} is taken with R_{16} to form a group having the structure:



37. A compound of claim 33, wherein R_{15} is taken with R_{16} to form a group having the structure:



38. A composition comprising an amount of a compound of claim 1 effective to modulate GSK3 activity in a human or animal subject when administered thereto, together with a pharmaceutically acceptable carrier.

39. A method of inhibiting GSK3 activity in a human or animal subject, comprising administering to the human or animal subject a composition of claim 33.

40. A method of treating a cell comprising administering to the cell an amount of a compound of claim 1 effective to inhibit GSK3 activity in the cell.

41. A method for treating a GSK3-mediated disorder in a human or animal subject, comprising administering to the human or animal subject an amount of a composition of claim 38 effective to inhibit GSK3 activity in the subject.

42. A method of claim 41, wherein the composition is administered by a mode of administration selected from the group consisting of oral, subcutaneous, transdermal, transmucosal, iontophoretic, intravenous, intrathecal, buccal, sublingual, intranasal, and rectal administration.

43. A method of claim 41, wherein said GSK3-mediated disorder is selected from the group consisting of diabetes, Alzheimer's disease, Parkinson's disease, Huntington's disease, obesity, atherosclerotic cardiovascular disease, essential hypertension, polycystic ovary syndrome, syndrome X, ischemia, traumatic brain injury, bipolar disorder, immunodeficiency and cancer.

44. A method of claim 43, which further comprises administering to the subject one or more additional active agents.

45. A method of claim 45, wherein the GSK3-mediated disorder is diabetes and the additional active agent is selected from the group consisting of insulin, troglitazone, rosiglitazone, pioglitazone, glipizide and metformin.

46. A compound of claim 1 for use as a pharmaceutical.

47. Use of a compound of claim 1 in the manufacture of a medicament for the treatment of diabetes, Alzheimer's disease, Parkinson's disease, Huntington's disease, obesity, atherosclerotic cardiovascular disease, essential hypertension, polycystic ovary syndrome, syndrome X, ischemia, traumatic brain injury, bipolar disorder or cancer.